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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,019	09/21/2001	Chikara Aizawa	SHIM1120	9316

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EXAMINER	
LE, EMILY M	

ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/830,019	AIZAWA ET AL.	
	Examiner	Art Unit	
	Emily Le	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on August 31, 2007

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on August 31, 2007 has been entered.

Status of Claims

2. Claims 4-6 and 8-15 are cancelled. Claim 1 has been amended. Claims 1-3 and 7 are pending and under examination.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-3 and 7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

In response to the previous office action, Applicant amended the claims to recite, "wherein the toxin is 95% pure". However, Applicant failed to points out where and/or how the originally filed disclosure supports the amendment.

While the claims refer to two different toxins, a natural toxin and a purified attenuated version of said toxin, it is presumed that the cited recitation is directed at the purity level of the attenuated toxin. In view of this, the Office examined the original disclosure and found that it does not support a 95% purity level for the attenuated toxin. In contrast, it is found that the original disclosure supports 95% purity level for the natural toxin rather than the attenuated toxin. See page 34, line 9 of the original disclosure. Hence, the claims are rejected for the presence of new matter.

Claim Rejections - 35 USC § 102

5. The anticipatory rejection is withdrawn in view of Applicant's response, which includes an amendment to the claims.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 3 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Germanier et al.

The claims are directed at a purified at 95% and attenuated cholera toxin having a residual toxic activity of less than 1/2000 that of the natural toxin, attenuated by incubation at 30 to 40 degrees Celsius, formalin bounded to lysine residues, and

wherein the natural serine, glutamic acid and lysine residues of the toxin is retained. Claim 3, which depends on claim 1, requires that the purified and attenuated toxin has the amino acid sequence of the natural toxin. Claim 7, which depends on claim 1, requires the residual toxic activity of **less than** 1/10000.

Germanier et al. teaches a purified and attenuated cholera toxin. The toxin of Germanier has a residual toxic activity of less than 1/2000 that of the natural toxin, attenuated by incubation at 30 to 40 degrees Celsius with formalin, and wherein the amino acid sequence of the toxin has not been modified.

The difference between the claimed toxin and the toxin of Germanier et al. is: it is not readily apparent if the purified and attenuated toxin of Germanier et al. is 95%.

However, at the time the invention was made, it would have been prima facie obvious for one of ordinary skill in the art to purify the attenuated toxin of Germanier et al. to the purest level. One of ordinary skill in the art, at the time the invention was made would have been motivated to do so to obtained a pure attenuated toxin. One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success for doing so because purification is routinely practiced.

It is noted that in response to the anticipation rejection, prior to the submission of the current claim listing, Applicant argues that the product of Germanier et al. is structurally different that than the claimed composition because of a difference in the incubation temperature. In response to Applicant's argument, it should be noted that the purified and attenuated toxin of Germanier et al. is incubated at the same

temperature range as claimed, at 30 degrees Celsius. See the Detoxification of cholera toxin section, disclosed on page 1693, of Germanier et al.

Regarding the limitation of claim 7, the difference between the invention encompassed by claim 7 and Germanier et al. is: The residual toxic activity of the purified and attenuated cholera toxin of Germanier et al. is noted to be 1/10000 that of its natural toxin. [Abstract] It is not readily apparent if the purified and attenuated cholera toxin of Germanier et al. is has a residual toxic activity of **less than** 1/10000 than its natural toxin.

However, MPEP § 2144.05 [R3] [II] states: Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held

to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

In the instant case, the specification does not contain any evidence indicating that the claimed level of toxicity is critical. Additionally, the general conditions of the claimed invention are disclosed by Germanier et al. Germanier et al. teaches the detoxification of the cholera toxin. Germanier et al. also suggests the administration of the detoxified toxin with whole cell vaccines against *Vibrio cholerae* infection. [First sentence, third paragraph, left column, page 1692] Thus, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to reduce the toxicity of the toxin to a level that ensure its safe use with whole cell vaccines against *Vibrio cholerae* infection.

8. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Germanier et al., as applied to claim 1, in view of Douce et al.[1]

Claim 2, which depends on claim 1, requires the purified and attenuated toxin to be a mutant, wherein one ore more amino acid residues are substituted, inserted, deleted or added, and having adjuvant activity, while the existing serine, glutamic acid and lysine residues are retained.

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[1] Douce et al. Intranasal immunogenicity and adjuvanticity of site-directed mutant derivatives of cholera toxin. Infection and Immunity, Vol. 65, No. 7,2821-2828.

As provided above, Germanier et al. teaches the purified and attenuated toxin of claim 1. However, Germanier et al. does not teach the substitution, insertion, deletion or addition of one or more amino acid residues of the purified and attenuated toxin.

Douce et al. teaches the substitution, insertion, deletion or addition of one or more amino acid residues of a toxin to modify the adjuvanticity and immunogenicity of the toxin while retaining the existing serine, glutamic acid and lysine residues.

Hence, it would have been prima facie obvious for one of ordinary skill in the art, at the time the invention was made, to have combine the teachings of Douce et al. and Germanier et al. One of ordinary skill in the art, at the time the invention was made, would have been motivated to do so to modify the adjuvanticity and immunogenicity of the purified and attenuated toxin of Germanier et al. One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success for doing so because Douce et al. teaches the modification of immunogenicity and adjuvanticity of a toxin by introducing mutation in the amino acid sequence of the mutant.

Conclusion

9. No claims are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Le whose telephone number is (571) 272 0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce R. Campell can be reached on (571) 272-0974. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Emily M. Le/
Patent Examiner
Art Unit 1648

/E.Le/